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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,099	04/07/2004	Simon McEwen	61190(50221)	8281

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EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	PAPER NUMBER
1651	
MAIL DATE	DELIVERY MODE
04/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/820,099	MCEWEN, SIMON	
	Examiner	Art Unit	
	SUSAN HANLEY	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24 and 29-31* is/are pending in the application.

4a) Of the above claim(s) *30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/8/08 has been entered.

Election/Restrictions

Applicant argues that since claim 29 has been indicated as allowable, dependent claim 30, a method of using claim, should be rejoined.

Claim 30 will not be rejoined at this time becasue the status of allowability of claim 29 is withdrawn for the reasons given below.

The election of claims 1-24 and 29; and mucopolysaccharidases as the enzyme specie in the reply filed on 4/5/07 are again acknowledged.

Claims 30 and 31 stand withdrawn.

Claim Rejections - 35 USC § 112

Claims 1-24 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. The status of allowable for claim 29 is withdrawn and the enablement rejection is reinstated for the reasons stated below.

The following is a reiteration of the grounds of rejection against claims 1-24 and 29 that was made in the Office action mailed 10/15/2007:

The claims are drawn to a therapeutic compostion for the treatment or prophylaxis of an autoimmune condition wherein the composition comprises an effective amount of an enzyme and an immunogen. Dependent claims define the enzyme as a beta-glucuronidase, the immunogen can be collagen, the composition can further comprise a stabilizer and/or activator as well as compounds that contain hydroxyl moieties.

The specification speculates that claimed composition down-regulates T-cell mediated reactions. The specification asserts that the claimed compostion can treat or prevent auto-immune diseases including rheumatoid arthritis (RA). An example of the efficacy of the claimed composition in a mouse model of RA is disclosed. Three groups of mice were injected with collagen. Groups A and C were treated with different strengths (group C receiving the higher dose) of the claimed composition while group B served as the control. The severity of the response to the collagen injection was by observation. The specification discloses that early on, the mice in group A had a somewhat lower incidence of the disease, and after day 29 there was no significant different between the control and the lower dose treatment group. The specification discloses that the higher dose group (group C) displayed a lower severity of RA during

the time course compared to the control and the levels of disease reaction are "within the range seen when established anti-arthritic drugs are given during the course of similar experiments" (p. 13). An Annova analysis of groups B vs. C was on the order of p=0.0196.

The disclosure has been carefully considered but it is not deemed as enabling the claims. The claimed compostion and its intended use for treating auto-immune diseases is an extension of enzyme-potentiated desensitization (EPD) which was developed by McEwen in the 1970's for allergy treatment. EPD and other forms of immunotherapy were recently reviewed by Terr (2004; previously cited). Terr notes that proponents of EPD claim that it has successfully treated allergic rhinitis as well as ulcerative colitis, IBS, chronic fatigue syndrome, hyperactivity, rheumatoid arthritis, etc. (p. 707).

However, Terr asserts that to date, there have been no published research finding in patients treated by this method to substantiate this theory. The effectiveness of enzyme-potentiated desensitization and the presumed pharmacological property of beta-glucuronidase on the immune system are based on anecdotal evidence only. Several published double-blind reports claim symptomatic improvements in adults or children with allergic rhinitis or asthma along with conflicting results of immunological changes. These studies have been done on 10 to 20 subjects only in the active and placebo groups, have been of short duration and generally lacked objective measurements of disease actiivty" (p. 707). Terr goes on to enumerate the numerous rules to avoid treatment failure. In a similar review in 1999, Terr noted that there were no published

studies to substantiate the hypothesis of the action of EPD on the immune system, wherein proponents of EPD assert that the therapy activated a new population of CD8 lymphocytes that suppress or down-regulate the response to injected Patients, thereby suppressing the immune response (p. 484).

Claims drawn to pharmaceutically acceptable compositions and to methods of administering said compositions to humans generally require supporting evidence because of the unpredictability in biological responses to therapeutic treatments. EPD has been reviewed in the literature and clear-cut evidence regarding its efficacy is not convincing. The instant application is an extension of EPD from its origin for the treatment of allergic rhinitis to the therapy of auto-immune diseases. The data provided by the examples does not substantiate the claims. There is no substantial difference between the control group and those mice receiving the lower does (group A). The data regarding groups B and C is not clear cut. The calculated correlation factor is low and the data in Figures 3 and 5 shows a great deal of overlap of data points. The specification relies on a nebulous conclusion (e.g., comparing the disclosed data with undisclosed data for unnamed RA treatments). Thus, the data presented by the specification does not appear to be a reliable indicator that the skilled artisan could use to a predict successful therapeutic outcome for a patient group that is known to be extremely difficult to treat. Furthermore, the review of human treatment records by the prior art casts doubt on EPD, in general.

There is no reliable method that predicts if EPD is effective in treating for preventing autoimmune diseases, including RA. The disclosure cannot be extrapolated

by the skilled artisan to predict if EPD will be effective to treat or prevent autoimmune diseases. It would require one of skill in the art undue experimentation to determine if EPD would be effective for the claimed treatment according to the directions of the instant disclosure. Thus, the claims are not enabled by the disclosure.

Regarding claim 29, the rejection is reinstated for the reasons stated above. Even if the claims were enabled by the disclosure, the composition of claim 29 is not the same as the composition administered to the RA mice in the examples. Firstly, the amount of beta-glucuronidase in the compostion of claim 29 is expressed in activity units (Fishman units/ml) while the amount in the example is 2 mg/ml. The is no indication of the specific activity of the enzyme in the example to determine if the amount of enzyme in the example actually corresponds to 1,000 to 5,000 Fishman units. The specific activity of a preparation of enzyme depends upon the method and no indication of specific activity is given in the specification.

Regarding the amounts of protamine sulfate and cyclohexane diol in the claimed compostion (6 µg/ml (1000 µg = 1 mg, thus this amount is the same as $6x10^{-3}$ mg/ml)) and 1 µg/ml ($6x10^{-3}$ mg/ml), respectively. The amounts of a composition of protamine sulfate and cyclohexane diol that is added to the enzyme compostion (hence, there is a dilution) in the examples are far less (6x10-5 mg/ml and 1x-8 mg/ml, respectively). Furthermore, the amount of the composition having the protamine sulfate and cyclohexane diol that is added to the enzyme solution is not specified in the example. Thus, there is no way to determine what the actual amounts of protamine sulfate and cyclohexane diol are in the example.

Hurwitz (US 2008/0314333) reports that the molecular weight of collagen is 5,000 to 10,000 Da (see claim 19). Assuming the higher molecular weight, 50 ng corresponds to 3.02 x 10^{12} molecules (50 ng x 1g/1x10^{9} ng x 1mole/10,000g x 6.02 x 10^{23} molecules/1mole). Even if the molecular weight was at the low end (5,500 g/mole), this would correspond to 5.5 x 10^{11} molecules. Neither of these values match any of those specified in claim 29.

Also, since a 1:1 mixture of the enzyme and collagen solution is administered, the final concentration of the chondroitin sulfate is 0.25 mg/ml which is not that as claimed in claim 29.

Thus, even if the specification was enabling (which it is not for the reasons stated above) the claimed compositions of claim 29, 1 or 11 are not commensurate with the enzyme/collagen compostion used in the examples which has the alleged unexpected result.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSAN HANLEY whose telephone number is (571)272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Susan Hanley/
Examiner, Art Unit 1651

/Sandra Saucier/
Primary Examiner, Art Unit 1651